14

PATENT COOPERATION TREATY

PCT

REC'D 23 OCT 2001
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1770-228PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00775	28/06/2000	29/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/56		
Applicant MCGILL UNIVERSITY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/12/2000	19.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heimann-Pohl, B Telephone No. +49 89 2399 8713

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00775

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

Sequence listing part of the description, pages:

1-10, filed with the letter of 02.10.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 9, 10.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 9, 10 are so unclear that no meaningful opinion could be formed (*specify*):
   se separate sh et

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-8
	No:	Claims	1-4
Inventive step (IS)	Yes:	Claims	
	No:	Claims	5-8
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1). The present application relates to an α1,2-mannosidase for specifically converting $Man_9GlcNAc$ to $Man_8GlcNAc$ isomer B encoded by SEQ ID NO: 18 and a mutant of said enzyme having an amino acid residue replacement from Arg to Leu at position 461 (R461L).

2). Priority (Box II)

The mutant R461L is not disclosed in the priority document. Thus claims 9 and 10 are not entitelt to the priority of 29.06.1999.

3). Prior Art

D1: LAL ANITA ET AL: 'Substrate specificities of recombinant murine Golgi alpha1,2-mannosidases IA and IB and comparison with endoplasmic reticulum and Golgi processing alpha1,2-mannosidases.' GLYCOBIOLOGY, vol. 8, no. 10, October 1998 (1998-10), pages 981-995, XP000952920 ISSN: 0959-6658
D2: DATABASE EMBL [Online] Accession AA631254, 31 October 1997 (1997-10-31) NCI-CGAP: 'nq81c12.s1 NCI_CGAP_Co9 Homo sapiens cDNA clone IMAGE:1158742 3' similar to WP:T03G11.4 CE04872 MAN(9)-ALPHA-MANNOSIDASE ;, mRNA sequence.' XP002150707 cited in the application
D3: WO 00 12708 A (BAKER KEVIN ;GENENTECH INC (US); GODDARD AUDREY (US); GURNEY AUSTI) 9 March 2000 (2000-03-09)
D4: WO 00 58473 A (CURAGEN CORP ;LEACH MARTIN (US); SHIMKETS RICHARD A (US)) 5 October 2000 (2000-10-05)
D5: WENG SHUAI ET AL: 'Evaluation of the early processing routes of N-linked oligosaccharides of glycoproteins through the characterization of Man- 8GlcNAc-2 isomers: Evidence that endomannosidase functions in vivo in the absence of a glucosidase blockade.' GLYCOBIOLOGY, vol. 6, no. 8, 1996, pages 861-868, XP000952947 ISSN: 0959-6658
D6: JAKOB CLAUDE A ET AL: 'Degradation of misfolded endoplasmic reticulum glycoproteins in Saccharomyces cerevisiae is determined by a specific oligosaccharide structure.' JOURNAL OF CELL BIOLOGY, vol. 142, no. 5, pages 1223-1233, XP002150705 ISSN: 0021-9525
D7: TREMBLAY LINDA O ET AL: 'Cloning and expression of a specific human alpha1,2-mannosidase that trims Man9GlcNAc2 to Man8GlcNAc2 isomer B during

N-glycan biosynthesis.' GLYCOBIOLOGY, vol. 9, no. 10, October 1999 (1999-10), pages 1073-1078, XP000952919 ISSN: 0959-6658
D8: GONZALEZ DANIEL S ET AL: 'Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis.' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 30, 23 July 1999 (1999-07-23), pages 21375-21386, XP002150706 ISSN: 0021-9258

4). Novelty, Inventive Step and Industrial Applicability (Box V)

4.1). Novelty (Art. 33(2) PCT)

Claim 1 lacks novelty over D4. Said document discloses sequences SEQ ID NO:3585 and SEQ ID NO: 3586. Sequence comparison revealed 99.9% identity in 2712 bp overlap between SEQ ID NO:3585 and SEQ ID NO:18 and 100% identity in 663 amino acid overlap between SEQ ID NO:3586 and SEQ ID NO:19.

D2 discloses an EST of a MAN(9)-alpha mannosidase, however the specific activity is not disclosed.

Claims 2-4 lack novelty over D5. The document reports that kifunensine and 1-deoxymannojirimycin have been shown to be potent inhibitors of the Golgi as well as the ER mannosidase I (page 865 right col. second paragraph and Figure 6). However, it must be remarked here that only the two inhibitors, kifunensine and 1-deoxymannojirimycin, mentioned in the present application could have been searched. No search could have been carried out to unknown agonists and antagonists these can thus also not be examined.
The same restriction has to be made for claims 5-8.

4.2). Inventive Step (Art. 33(3) PCT)

Even if the subject matter of claim 1 were novel it would apparently lack an inventive step over the over the combination of D1 and D5. D1 discloses α1,2-mannosidase for specifically converting $Man_9GlcNAc$ to $Man_8GlcNAc$ isomer B

(abstract, page 986). D5 further discloses that on page 864 that "Confirmation that Golgi mannosidase I processes $Man_9GlcNAc$ to the B-isomer of $Man_8GlcNAc$ was obtained by isolating the oligosaccharide formed after brief incubation with purified rat liver Golgi membranes.". Although said enzymes were not cloned, recombinantly expressed and sequenced in said documents they clearly provide an incentive to do so. Thus isolation of these enzymes was obvious to try and with a reasonable expectation of success. Consequently, claim 1 and also claims 5-8 seem to lack an inventive step.

4.3). Industrial Applicability

For the assessment of the present claims 5-8 and 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5). No Examination (Box III) in connection with Clarity (Box VIII)

Art. 6 PCT requires the matter for which protection is sough be defined in the claims be defined in a clear and concise manner and that the claims be supported by the description. This means not only that a claim must be non-ambiguous and comprehensible, but also that **all the essential features** of the claimed invention have to be indicated in the claim, these being the features which are necessary in order **to obtain the desired effect**. the essential technical features may also be expressed in general functional terms, if, from an objective point of view, such features cannot otherwise be defined more precisely without restricting the scope of the claim, and **if these features provide instructions which are sufficiently clear for the skilled person to reduce them into practice without undue burden**, ie with no more than a reasonable amount of experimentation, and without applying inventive skill.
It should be noted that qu stions f clarity and support may aff ct issues

under Art. 33 (2), Art. 33 (3) or Art. 5 PCT.

Claims 9 and 10 lack clarity. The α1,2-mannosidase polypeptide consists of 699 amino acids. To find out which position has to be altered over the whole length and replaced by one of the other amino acids to provide a mutant to produce altered recombinant glycoproteins with improved uptake is considered as undue burden of experimentation. Thus said claims are contravening the requirements of Art. 6 PCT. Since the mutant is not defined as R461L the requirement that the claims must be clear when examined in isolation is not fulfilled. (R461L also seems to be novel and inventive over the relevant prior art.)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rul s 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
1770-228PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00775	28/06/2000	29/06/1999
Applicant		
MCGILL UNIVERSITY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

HUMAN ALPHA 1,2-MANNOSIDASE

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00775

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00775

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/56 C12N9/24 C12P21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, EMBL, STRAND, WPI Data, PAJ, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LAL ANITA ET AL: "Substrate specificities of recombinant murine Golgi alpha1,2-mannosidases IA and IB and comparison with endoplasmic reticulum and Golgi processing alpha1,2-mannosidases." GLYCOBIOLOGY, vol. 8, no. 10, October 1998 (1998-10), pages 981-995, XP000952920 ISSN: 0959-6658 abstract page 986, left-hand column, last paragraph -right-hand column, paragraph 1 page 989, right-hand column figure 11 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2000	27. 10. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lejeune, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WENG SHUAI ET AL: "Evaluation of the early processing routes of N-linked oligosaccharides of glycoproteins through the characterization of Man-8GlcNAc-2 isomers: Evidence that endomannosidase functions in vivo in the absence of a glucosidase blockade." GLYCOBIOLOGY, vol. 6, no. 8, 1996, pages 861-868, XP000952947 ISSN: 0959-6658 abstract page 865, right-hand column, paragraph 2 page 864, left-hand column, last line -right-hand column, paragraph 1 figure 6 ---	2-4
A	DATABASE EMBL [Online] Accession AA631254, 31 October 1997 (1997-10-31) NCI-CGAP: "nq81c12.s1 NCI_CGAP_Co9 Homo sapiens cDNA clone IMAGE:1158742 3' similar to WP:T03G11.4 CE04872 MAN(9)-ALPHA-MANNOSIDASE ;, mRNA sequence." XP002150707 cited in the application 96.7% identity in 880 BP overlap with SEQ ID NO 18 ---	1
A	JAKOB CLAUDE A ET AL: "Degradation of misfolded endoplasmic reticulum glycoproteins in Saccharomyces cerevisiae is determined by a specific oligosaccharide structure." JOURNAL OF CELL BIOLOGY, vol. 142, no. 5, pages 1223-1233, XP002150705 ISSN: 0021-9525 abstract ---	5-10
P,X	TREMBLAY LINDA O ET AL: "Cloning and expression of a specific human alpha1,2-mannosidase that trims Man9GlcNAc2 to Man8GlcNAc2 isomer B during N-glycan biosynthesis." GLYCOBIOLOGY, vol. 9, no. 10, October 1999 (1999-10), pages 1073-1078, XP000952919 ISSN: 0959-6658 the whole document --- -/--	1-4

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GONZALEZ DANIEL S ET AL: "Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 30, 23 July 1999 (1999-07-23), pages 21375-21386, XP002150706 ISSN: 0021-9258 the whole document ---	1-4
P,X	WO 00 12708 A (BAKER KEVIN ;GENENTECH INC (US); GODDARD AUDREY (US); GURNEY AUSTI) 9 March 2000 (2000-03-09) page 3 page 46 -page 48 figures 9,10; example 8 100% identity between the AA sequence of PRO1477 and SEQ ID 19. 99.9% identity between the nucleic acid sequence of PRO1477 and SEQ ID 18 ---	1
E	WO 00 58473 A (CURAGEN CORP ;LEACH MARTIN (US); SHIMKETS RICHARD A (US)) 5 October 2000 (2000-10-05) page 231 99.9% identity in 2712 BP overlap between SEQ ID 3585 of WO0058473 and SEQ ID NO 18 100% identity in 663 AA overlap between SEQ ID 3586 of WO0058473 and SEQ ID NO 19 -----	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/00775

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0012708 A	09-03-2000	AU 5590899 A	21-03-2000
		AU 6041399 A	10-04-2000
		WO 0017353 A	30-03-2000
WO 0058473 A	05-10-2000	NONE	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
COTE, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

Date of mailing (day/month/year) 11 January 2001 (11.01.01)	
Applicant's or agent's file reference 1770-228PCT	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/CA00/00775	28 June 2000 (28.06.00)	29 June 1999 (29.06.99)

Applicant
MCGILL UNIVERSITY et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AG,AU,BZ,DZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   11 January 2001 (11.01.01) under No. WO 01/02586

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COTE, France et al
SWABEY OGILVY RENAULT
1981, Avenue McGill College
Bureau 1600
Montréal, Québec H3A 2Y3
CANADA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.10.2001
Applicant's or agent's file reference 1770-228PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00775	28/06/2000	29/06/1999

Applicant
MCGILL UNIVERSITY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Guerin, A Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1770-228PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00775	28/06/2000	29/06/1999

International Patent Classification (IPC) or national classification and IPC
C12N15/56

Applicant
MCGILL UNIVERSITY et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/12/2000	19.10.2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00775

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-10 as originally filed

Drawings, sheets:

1/9-9/9 as originally filed

Sequence listing part of the description, pages:

1-10, filed with the letter of 02.10.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 9, 10.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 9, 10 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 5-8
	No:	Claims 1-4
Inventive step (IS)	Yes:	Claims
	No:	Claims 5-8
Industrial applicability (IA)	Yes:	Claims 1-4
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1). The present application relates to an α1,2-mannosidase for specifically converting $Man_9GlcNAc$ to $Man_8GlcNAc$ isomer B encoded by SEQ ID NO: 18 and a mutant of said enzyme having an amino acid residue replacement from Arg to Leu at position 461 (R461L).

2). Priority (Box II)

The mutant R461L is not disclosed in the priority document. Thus claims 9 and 10 are not entitelt to the priority of 29.06.1999.

3). Prior Art

D1: LAL ANITA ET AL: 'Substrate specificities of recombinant murine Golgi alpha1,2-mannosidases IA and IB and comparison with endoplasmic reticulum and Golgi processing alpha1,2-mannosidases.' GLYCOBIOLOGY, vol. 8, no. 10, October 1998 (1998-10), pages 981-995, XP000952920 ISSN: 0959-6658
D2: DATABASE EMBL [Online] Accession AA631254, 31 October 1997 (1997-10-31) NCI-CGAP: 'nq81c12.s1 NCI_CGAP_Co9 Homo sapiens cDNA clone IMAGE:1158742 3' similar to WP:T03G11.4 CE04872 MAN(9)-ALPHA-MANNOSIDASE ;, mRNA sequence.' XP002150707 cited in the application
D3: WO 00 12708 A (BAKER KEVIN ;GENENTECH INC (US); GODDARD AUDREY (US); GURNEY AUSTI) 9 March 2000 (2000-03-09)
D4: WO 00 58473 A (CURAGEN CORP ;LEACH MARTIN (US); SHIMKETS RICHARD A (US)) 5 October 2000 (2000-10-05)
D5: WENG SHUAI ET AL: 'Evaluation of the early processing routes of N-linked oligosaccharides of glycoproteins through the characterization of Man- 8GlcNAc-2 isomers: Evidence that endomannosidase functions in vivo in the absence of a glucosidase blockade.' GLYCOBIOLOGY, vol. 6, no. 8, 1996, pages 861-868, XP000952947 ISSN: 0959-6658
D6: JAKOB CLAUDE A ET AL: 'Degradation of misfolded endoplasmic reticulum glycoproteins in Saccharomyces cerevisiae is determined by a specific oligosaccharide structure.' JOURNAL OF CELL BIOLOGY, vol. 142, no. 5, pages 1223-1233, XP002150705 ISSN: 0021-9525
D7: TREMBLAY LINDA O ET AL: 'Cloning and expression of a specific human alpha1,2-mannosidase that trims Man9GlcNAc2 to Man8GlcNAc2 isomer B during

N-glycan biosynthesis.' GLYCOBIOLOGY, vol. 9, no. 10, October 1999 (1999-10), pages 1073-1078, XP000952919 ISSN: 0959-6658
D8: GONZALEZ DANIEL S ET AL: 'Identification, expression, and characterization of a cDNA encoding human endoplasmic reticulum mannosidase I, the enzyme that catalyzes the first mannose trimming step in mammalian Asn-linked oligosaccharide biosynthesis.' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 30, 23 July 1999 (1999-07-23), pages 21375-21386, XP002150706 ISSN: 0021-9258

4). Novelty, Inventive Step and Industrial Applicability (Box V)

4.1). Novelty (Art. 33(2) PCT)

Claim 1 lacks novelty over D4. Said document discloses sequences SEQ ID NO:3585 and SEQ ID NO: 3586. Sequence comparison revealed 99.9% identity in 2712 bp overlap between SEQ ID NO:3585 and SEQ ID NO:18 and 100% identity in 663 amino acid overlap between SEQ ID NO:3586 and SEQ ID NO:19.

D2 discloses an EST of a MAN(9)-alpha mannosidase, however the specific activity is not disclosed.

Claims 2-4 lack novelty over D5. The document reports that kifunensine and 1-deoxymannojirimycin have been shown to be potent inhibitors of the Golgi as well as the ER mannosidase I (page 865 right col. second paragraph and Figure 6). However, it must be remarked here that only the two inhibitors, kifunensine and 1-deoxymannojirimycin, mentioned in the present application could have been searched. No search could have been carried out to unknown agonists and antagonists these can thus also not be examined.
The same restriction has to be made for claims 5-8.

4.2). Inventive Step (Art. 33(3) PCT)

Even if the subject matter of claim 1 were novel it would apparently lack an inventive step over the over the combination of D1 and D5. D1 discloses α1,2-mannosidase for specifically converting $Man_9GlcNAc$ to $Man_8GlcNAc$ isomer B

(abstract, page 986). D5 further discloses that on page 864 that "Confirmation that Golgi mannosidase I processes $Man_9GlcNAc$ to the B-isomer of $Man_8GlcNAc$ was obtained by isolating the oligosaccharide formed after brief incubation with purified rat liver Golgi membranes.". Although said enzymes were not cloned, recombinantly expressed and sequenced in said documents they clearly provide an incentive to do so. Thus isolation of these enzymes was obvious to try and with a reasonable expectation of success. Consequently, claim 1 and also claims 5-8 seem to lack an inventive step.

4.3). Industrial Applicability

For the assessment of the present claims 5-8 and 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5). No Examination (Box III) in connection with Clarity (Box VIII)

Art. 6 PCT requires the matter for which protection is sough be defined in the claims be defined in a clear and concise manner and that the claims be supported by the description. This means not only that a claim must be non-ambiguous and comprehensible, but also that **all the essential features** of the claimed invention have to be indicated in the claim, these being the features which are necessary in order **to obtain the desired effect**. the essential technical features may also be expressed in general functional terms, if, from an objective point of view, such features cannot otherwise be defined more precisely without restricting the scope of the claim, and **if these features provide instructions which are sufficiently clear for the skilled person to reduce them into practice without undue burden**, ie with no more than a reasonable amount of experimentation, and without applying inventive skill.
It should be noted that questions of clarity and support may affect issues

under Art. 33 (2), Art. 33 (3) or Art. 5 PCT.

Claims 9 and 10 lack clarity. The α1,2-mannosidase polypeptide consists of 699 amino acids. To find out which position has to be altered over the whole length and replaced by one of the other amino acids to provide a mutant to produce altered recombinant glycoproteins with improved uptake is considered as undue burden of experimentation. Thus said claims are contravening the requirements of Art. 6 PCT. Since the mutant is not defined as R461L the requirement that the claims must be clear when examined in isolation is not fulfilled. (R461L also seems to be novel and inventive over the relevant prior art.)